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Rehabilitation

Principal Investigator: Corcos, Daniel M
Grant Number: 5R01NS040902-05
Title: STN STIMULATION--NEURAL CONTROL OF MOVEMENT AND POSTURE

Abstract: High frequency stimulation of the subthalamic nucleus (STN) dramatically improves all of the clinical motor symptoms of Parkinson's Disease (PD). However, there are limited objective data available to determine which characteristics of movement and posture are affected by STN stimulation, and by what neural mechanisms this is accomplished. The long-term objective of this application is to obtain objective neurophysiological data relating to the mechanisms by which effective STN stimulation alters the spatial and temporal patterns of activity mediating planned movement and posture in humans. Patients in whom STN surgery is successful, as defined by a 30% reduction in the motor score of the Unified Parkinson's Disease Rating Scale, will take part in a series of experiments designed to investigate the neural control of movement and posture. The experiments in Aim I will use electromyographic (EMG) and motion analysis techniques to identify which aspects of strength, movement and standing balance are improved, worsened or unchanged by STN stimulation. The effects of STN stimulation will also be compared with the effects of medication on the control of strength and movement. The hypothesis is that neither STN stimulation nor medication normalizes the control of movement, and STN stimulation does not normalize the control of standing balance. Aim 2 will use electroencephalographic (EEG) techniques to test whether STN stimulation-induced changes in movement and gait initiation are accompanied by changes in the spatial and temporal patterns of cortical activity in response to both internally and externally generated cues to move. The hypothesis is that STN stimulation does not normalize the pathways that are normally influenced by the STN but does allow other pathways to compensate better. Aim 3 will combine EEG techniques with stimulation through the quadripolar electrodes implanted in the region of the STN to examine the pathways activated by effective STN stimulation. The findings of the proposed experiments will advance our understanding of the role of the STN in motor function, assist in the development of improved models of the role of the basal ganglia in the control of movement and posture, and thereby contribute to improved treatments for Parkinson's disease. -

Principal Investigator: Cronin-Golomb, ALICE M.
Grant Number: 5R21NS043730-02
Title: Optic Flow and Spatial Navigation in Parkinson's Disease

Abstract: Parkinson's disease (PD) is a common age-related neurodegenerative disorder in which multiple aspects of visuospatial cognitive function are impaired, including spatial navigation. Deficits in spatial navigation arise from pathological changes in high-order association areas of the brain but also from defective input from lower-level visual processing areas, including those that mediate optic flow. Optic flow refers to the radial visual patterns that indicate a person's direction of self-movement and maintain gait and postural integrity. The status of optic flow perception in PD is unknown, as is its relation to PD deficits in spatial navigation, such as the inability to maintain a straight path while walking. We propose to examine optic flow perception in PD and its relation to spatial navigation. A critical focus is on the side of onset of motor impairment, contralateral to the hemisphere with predominant basal ganglia dysfunction. PD usually has unilateral onset, and many visuospatial abnormalities arise from right-hemisphere dysfunction. Our preliminary studies suggest that PD patients with left motor onset experience spatial compression of the left visual hemifield, which affects their ability to understand spatial relations and to use spatial information for navigation. We predict that deficits in optic flow perception underlie this perceived spatial compression. Specifically, hemifield differences in optic flow velocities lead patients to misperceive a straight path as curved toward the compressed side of space, and they "correct" their trajectory by walking a curved path. We propose to investigate optic flow and spatial navigation in 18 patients with left-onset PD, 18 with right-onset PD, 18 healthy elderly adults, and 18 healthy young adult adults. Our specific aims are: (1) To manipulate the speed of optic flow in the two visual hemifields and measure each participant's perception of relative speed, which is associated with perceived direction of self-motion. (2) To relate optic flow to spatial navigation. We will use a head-mounted system that provides virtual visual input and records the orientation and spatial position of the participant while walking through veridical space. (3) To relate optic flow and spatial navigation to daily function, as assessed with questionnaires. Our project is conceptually innovative in proposing optic flow deficiencies as a cause of problems of spatial navigation in PD and will generate pilot data in this potentially important area. We have forged novel collaborations between experts in visual psychophysics, behavioral neuroscience, biomedical engineering, and physical therapy to accomplish the goals of this project.-

Principal Investigator: FARLEY, BECKY G
Grant Number: 5R21NS043711-02
Title: Think big, from voice to limb movement rehabilitation

Abstract: We will test the efficacy of an innovative treatment technique that could induce a radical paradigm shift in movement rehabilitation for people with Parkinson disease (PD). Based upon an extremely successful speech treatment for people with idiopathic PD (the Lee Silverman Voice Treatment (LSVT(R)), people with PD will undergo intensive practice of high effort/large amplitude arm movements and learn to transfer their "big effort" to everyday movements. Unlike other physical therapy approaches with unclear efficacy, the LSVT(R) approach has clearly demonstrated both short and long term efficacy up to two years. In addition, LSVT(R) is supported by hypotheses put forth to explain hypokinesia and bradykinesia in people with PD, therefore, it is easily applied to limb movements. Fifty subjects will be randomly assigned to one of two interventions with similar intensity regimens, think big therapy (novel) or traditional physical therapy (control). Speech studies have shown that a treatment with a simple focus (think loud) may generalize to affect motor output in other systems (e.g., articulation, speaking rate, swallowing, respiratory mechanics). Thus, we predict that learning to perform bigger arm movements will also improve arm speed, based upon the well described relationship between movement speed and amplitude. In addition, we will document the generalizability of this technique to improve arm and leg function. Although both groups may show improvements given the intense work schedule, we predict that improvements in the think big therapy will be greater than in the traditional physical therapy (control) group. Measurements will include physiological tests for assessing arm movement speed and amplitude using kinematic techniques. As "sense of effort" is the primary proposed mechanism underlying this treatment approach, we will measure sense of effort. Additional measurements will include tests of arm and leg function (strength, timed ADL tasks, gait, handwriting), a standardized clinical assessment (UPDRS), and a subjective rating scale. If successful, we plan to 1) further validate retention of treatment effects and generalizability of this technique (speech to limb; limb to speech) and 2) develop a standardized protocol that can be used for training physical therapists.-

Principal Investigator: FILOTEO, J V
Grant Number: 5R01NS041372-03
Title: Striatal Contributions to Category Learning

Abstract: Previous studies indicate that patients with damage to the striatum, such as patients with Parkinson's disease (PD) or Huntington's disease (HD), are impaired in certain categorization tasks, but show no impairment in other categorization tasks. These studies suggest that the striatum may be involved in category learning under some circumstances but not others. One possible role of the striatum in category learning is that these structures are involved in learning nonverbal rules, but only when learning is based on corrective feedback under supervised learning conditions. Such a hypothesis is consistent with current models of striatal functioning. However, it is difficult to draw strong conclusions regarding the proposed role of the striatum based on past work because most of these studies used very different categorization tasks that vary along a number of important dimensions. The proposed research remedies these problems by conducting highly systematic studies of category learning in patients with PD. Factors known to impact the verbalizability of categorization rules will be explored, including (1) whether the rule is linear or nonlinear, (2) whether the rule requires information integration across dimensions or selective attention, and (3) whether the stimulus dimensions are separable or integral. In addition, the nature of training (corrective feedback or observation) will also be examined. These factors likely determine the extent to which the striatum is involved in category learning. Each of these factors will be explored within the framework of a highly successful categorization paradigm that has been used extensively in studies of normal cognition, and recently has been extended to some patient populations and normal aging. The paradigm, called the perceptual categorization task, is rigid enough that strong controls can be placed on factors that vary widely across other tasks, but is flexible enough that each of the factors outlined above can be studied in isolation. Further, quantitative models will be applied to the data of PD patients and controls in order to determine more precisely the nature of any observed category learning deficits in the PD patients. -

Principal Investigator: Hallett, Mark
Grant Number: 5Z01NS002669-20
Title: Physiological Analysis Of Voluntary Movement

Abstract: Unavailable

Principal Investigator: HORTOBAGYI, TIBOR
Grant Number: 1R13NS047105-01
Title: International Symposium on Motor Control Using TMS

Abstract: This application is a single-year request of support for an international symposium, "Mechanisms of Movement and Sensation Using Transcranial Magnetic Stimulation" (TMS) as part of the XVth biennial Congress of the International Society of Electrophysiology and Kinesiology (ISEK), Boston, June 18-21, 2004. The rationale for the symposium is that in this era of specialization, research subdisciplines on the one hand and basic researchers and therapists on the other, tend to separate. This symposium is an effort to minimize this separation. The symposium's aim is to generate a novel synthesis of basic science and clinical mechanisms of motor cortex plasticity and thus facilitate the design of rehabilitation programs. Pascual-Leone, co-chair, (US), will provide a historical perspective on TMS and rTMS. Valero Cabre (US) will discuss the effects of TMS and rTMS on the basic electrophysiological and metabolic properties of cortical neurons with reference to Parkinson's disease. Hortobagyi (US) will discuss the contralateral organization of the human nervous system. Taylor (Australia) will address the mechanisms of central fatigue in polio and chronic fatigue syndrome. Sawaki (US) will present on training dependent plasticity of the motor cortex as evidence for short-term motor memory, specifically in stroke. Rothwell (UK) will address the effect of afferent input on motor cortex organization and plasticity in healthy subjects and in patients with dystonia and hand cramps. Manto (Belgium) as co-chair will moderate the discussions. The symposium will provide maximal interaction between speakers and attendees as it will take place in a plenary session format as the only ongoing session. Through student discounts, it will provide an economical opportunity for biomedical trainees to attend. The presentations will be published in IEEE Engineering in Medicine and Biology, making a substantial impact on the field by attracting the interest of neurologists, clinical neurophysiologists, basic and clinical movement and sensation neuroscientists, physical therapists, biomechanists, biomedical engineering researchers, roboticists, educators and students from the US and abroad.-

Principal Investigator: LAU, YUEN-SUM
Grant Number: 5R01NS047920-02
Title: Impact of Exercise on Parkinson's Disease Therapy

Abstract: Parkinson's disease (PD) is a slow, progressive, debilitative, neurodegenerative disease, which has no cure. The current pharmacological therapies only temporarily mask symptoms, but do not protect neurons from further degeneration. Furthermore, chemotherapeutic agents often cause severe adverse effects and reduce the effectiveness of treatment. Numerous clinical reports have suggested that endurance exercise can slow down disease progression, and add years of independent and quality life to PD patients, or even improve the delivery and efficacy of L-DOPA treatment. Exercise therapy, or in conjunction with drug therapy at early onset of disease state, have been highly advocated by recent clinical trials. The potential health benefit and neurological mechanisms of action for exercise on PD rehabilitation have not been rigorously tested in the laboratory animal models. This research is designed to elucidate the impact of endurance exercise training on nigrostriatal dopamine (DA) neuron plasticity using a slow, progressive, and neurodegenerative mouse model of PD developed and characterized by our laboratory. This model is established based on a regimen of chronic 1-Methyl-4-phenyl - 1,2,3,6-tetrahydropyridine (MPTP) injections co-administered with probenecid, a drug that inhibits the peripheral and neuronal clearance of MPTP and potentiates the neurotoxicity of MPTP. In this model, we observed a marked decrease of nigrostriatal DA function within one week after treatment and remained low for 6 months. The animal also shows a gradual loss of substantia nigra (SN) neurons, decline of motor activity, and an accumulation of c-synuclein-immunoreactive inclusions in the SN. We further present in the application our preliminary findings supporting the feasibility and potential neuromodulatory role of endurance exercise on enhancing nigrostriatal DA transmission and PD rehabilitation using this model. In this research, we will test the following hypotheses centered on the endurance exercise, when administered at an early stage in the parkinsonian (PK) mice, will 1) improve their mobility and physical rehabilitation, 2) improve the efficacy of L-DOPA, 3) produce these effects by mechanistically causing an elevation of BDNF expression, an increase in the differentiation of DA progenitor cells, and an enhanced DA transmission and plasticity in the nigrostriatal neurons. Findings from this research should provide new insight into the development of alternative therapeutic approaches for enhancing the conventional pharmacological treatment and rehabilitation of PD. Potential benefits for using such a synergistic approach in managing PD would likely reduce the risk of drug toxicity and lower the cost of health

Principal Investigator: O'DONNELL, MARTHA E
Grant Number: 1R13NS049949-01
Title: 2004 Barriers of CNS

Abstract: This proposal is a request for funds toward support of the 3rd "Barriers of the CNS" Gordon Research Conference to be held June 27th to July 2nd 2004 in Tilton, NH. Funds are also requested for support of the 4th and 5th conferences, to be held in 2006 and 2008. This Gordon Research Conference was initiated as a catalyst for interaction among researchers from a variety of disciplines working on issues of blood-brain-barrier (BBB) and blood-CSF barrier in health and disease. Research in this area is already leading to development of new therapeutic approaches for the treatment of stroke, head trauma, neurodegeneration, brain inflammation and brain tumors, to name a few. Although portions of these areas of investigation are represented at several national and international research meetings, there have been few opportunities for scientists working in the field to come together with a specific concentrated focus on issues related to barriers of the CNS. The upcoming 2004 conference will include issues related to the physiology and pathophysiology of the BBB and blood-CSF barriers as well as the delivery of drug and gene therapies to the CNS. A new aspect of the 2004 meeting will be consideration of the neurovascular unit and how BBB cells interact with other cells in the neural environment. It is especially noteworthy that blood-brain barrier research has been identified by NIH as a critical area for development. Consistent with this, the mission of the Barriers of the CNS Gordon Research Conferences is to provide a forum for scientists with a variety of backgrounds and experience to share unpublished findings and work together to identify new strategies for attacking the many remaining unanswered questions with respect to the BBB and blood/CSF barriers. To this end, eminent scientists from both academia and the pharmaceutical industry are being brought together for an exciting "leading edge" meeting. Speakers have been selected on the basis of their eminence in the field and their communication skills. They are drawn from a wide geographical background. Chairs of the sessions have been selected on the basis of their considerable eminence and experience in the field and a known ability to communicate and debate well. In addition the presentation of posters is being vigorously encouraged especially by young postdoctoral and research students. It is expected that a considerable proportion of any NIH grant will be used to fund the attendance of young scientists and chairs. Two open workshops/debates to occur during the meeting are also planned. The maximum permitted attendance at this meeting is 150 scientists. -

Principal Investigator: POIZNER, HOWARD
Grant Number: 2R01NS036449-05A1
Title: Motor Control Deficits in Parkinson's Disease

Abstract: Our findings in the current grant period have led us to hypothesize that a major difficulty for patients with Parkinson disease (PD) is in assembling and using new sensorimotor mappings or coordinations. These process play a major role both in ongoing motor performance and in the acquisition of new skills, in addition, our preliminary data are consistent with a general observation that these processes may be relatively resistant to current therapeutic modalities. Furthering our understanding of this deficit, examining its impact on motor learning, and investigating the ability of dopaminergic therapy to reverse this deficit are the guiding aims of this proposal. The present proposal presents three experiments that are designed to confirm and extend our hypothesis and to investigate the degree to which dopaminergic therapy is able to remediate these deficits. The first two experiments (Specific Aims 1 and 2) introduce the requirement that subjects learn to move within a virtual environment as a prerequisite to establishing the new sensorimotor coordinations necessary for accurate target acquisition. We require subjects to master distortions which create discrepancies between the apparent (virtual) and real (proprioceptively signaled) location of their arms and to generalize the resulting learning to untrained regions of this environment. By dissociating movements from their normal sensory correspondences, we will challenge subjects' abilities to reconfigure their sensorimotor coordinations. The third experiment (Specific Aim 3) challenges patients by requiring them to integrate different motor acts in order to acquire visually-presented, real targets by compensating for a mechanical perturbation of the trunk during a trunk-assisted reach. We have integrated and coupled our previously developed system for analysis and display of three dimensional movements with our newly developed virtual reality environment. We will examine not only subjects' accuracy, but also the path, timing, and structure of their movements under different conditions and types of imposed distortions, in order to measure both performance and learning when PD patients are OFF versus ON dopaminergic therapy. By contrasting the performance and capacities of PD patients on and off dopaminergic therapy to that of comparable normals, we can both obtain clues as to how to overcome PD dysfunction and gain an insight into the key role of the basal ganglia in movement.-

Principal Investigator: STELMACH, GEORGE E
Grant Number: 5R01NS043502-02
Title: Joint Discoordination in Parkinson's Disease

Abstract: Unavailable